Article

Feline urate urolithiasis

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Abstract — This retrospective case control study describes associations between feline urate urolithiasis and breed, age, gender, and urine composition. Data from cases of feline uroliths submitted to the Canadian Veterinary Urolith Centre (CVUC) between February 2, 1998 and July 7, 2007 were reviewed. There were 10 083 feline uroliths examined, including 385 ammonium urate, 13 uric acid, and 21 mixed struvite/urate uroliths. The Egyptian Mau, Birman, and Siamese breeds were significantly predisposed to urate urolithiasis [odds ratio (OR) = 118, 95% confidence interval (CI) = 38.2 to 510, $P < 0.001$], (OR = 9.1, 95% CI = 2.0 to 32, $P < 0.001$) and (OR = 3.9, 95% CI = 2.5 to 5.9, $P < 0.001$), respectively. Urate urolithiasis was more frequent in younger cats (mean age 6.3 versus 7.1 y in cats with other uroliths, $P < 0.0001$) and in male cats ($P = 0.024$). The association between Egyptian Maus and urate urolithiasis was remarkable. The association in Siamese cats is consistent with prior reports, and the association with Birman cats requires further study.

Résumé — Urolithiase d'urate féline. Cette étude rétrospective de cas témoins décrit les associations entre l'urolithiase d'urate féline et la race, l'âge, le sexe et la composition de l'urine. Les données de cas d'urolithes félins soumis au Centre canadien vétérinaire d'urolithiase (CCVU) entre le 2 février 1998 et le 7 juillet 2007 ont été examinées. On a examiné 10 083 urolithes félins, incluant 385 d'urate d'ammonium, 13 d'acide urique et 21 d'urolithes mélangés d'urate/struvite. Les chats de races Mau égyptien, Birman et Siamois présentaient une prédisposition significative à l'urolithiase d'urate [rapport de cotes (RC) = 118, 95 % intervalle de confiance (IC) = 38,2 à 510, $P < 0,001$], (RC = 9,1, 95 % IC = 2,0 à 32, $P < 0,001$) et (RC = 3,9, 95 % IC = 2,5 à 5,9, $P < 0,001$), respectivement. L'urolithiase d'urate était plus fréquente chez les jeunes chats (âge moyen de 6,3 ans contre 7,1 ans chez les chats avec d'autres urolithes, $P < 0,0001$) et chez les chats mâles ($P = 0,024$). L'association entre les Maus égyptiens et les urolithiases d'urate était remarquable. L'association chez les chats Siamois était conforme à celle présentée dans des rapports antérieurs et l'association chez les chats Birmans exige de nouvelles études.

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Introduction

Uroliths are aggregates of crystalline and matrix material that form in one or more locations within the urinary tract when urine becomes oversaturated with crystallogenic substances, and may be composed of one or more mineral types (1). Compared to struvite and oxalate, the prevalence of urate urolithiasis in cats is low (2–4) and does not appear to have changed significantly in the last 2 decades.

One study of 20 343 feline uroliths reported that 5.6% were composed of uric acid and urate (2). This is consistent with prior studies reporting rates of 3.1% (3) to 6.3% (5). In a more recent study of 5230 feline uroliths and urethral plugs, stones which contained a component of urate were identified in 507 submissions (10%) (6). While less common than calcium oxalate and struvite uroliths, urate uroliths can nonetheless be important considering the number of cats that develop urolithiasis.

In dogs, reported breed predilections include dalmatians (7–10,13), English bulldogs, miniature schnauzers, shih tzus, Yorkshire terriers (9–12), and Russian black terriers (14). Pure

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Table 1. Summary of urate and struvite submissions showing gender and breed prevalence

Stone type	Number of submissions	Male (%)	Female (%)	Breed prevalence (%)	Breed odds ratio (95% CI) for urate submissions
Ammonium urate	385	220 (57%)	165 (43%)	Egyptian Mau 14/17 (82%)	118 (38.2–510)
				Siamese 25/190 (13%)	3.9 (2.5–5.9)
Uric acid	13	11 (85%)	2 (15%)	Birman 3/11 (27%)	9.1 (2.0–32)
Struvite	4364	1870 (43%)	2494 (57%)	NA	NA

CI — confidence interval, NA — not applicable.

urate uroliths occur more often in male dogs than females (11,13,15–17).

Siamese cats have significantly more urate containing calculi, and Persian cats significantly fewer (3,6), but there has been minimal investigation of factors associated with urate urolithiasis in cats. The purpose of this study was to describe associations between feline urate urolithiasis and breed, age, gender, and urine composition.

Materials and methods

The mineral composition of uroliths submitted to the Canadian Veterinary Urolith Centre (CVUC) was evaluated. Uroliths are submitted by veterinary practitioners for quantitative evaluation predominantly from across Canada; a small number of submissions come from the United States. Only submissions from a single episode of urolithiasis were included. Only uroliths from the first episode of urolithiasis were included if more than 1 urolith was submitted from an individual animal during the study period (recurrence of urolithiasis). All uroliths submitted for any given episode were analyzed.

To determine the mineral composition, each layer of each specimen was analyzed by optical crystallography, using polarized light microscopy. If additional clarification was needed, another quantitative technique was used, such as X-ray microanalysis, Fourier transformation infrared spectroscopy, or scanning electron microscopy. For this study, records of all feline urolith submissions from February 2, 1998 to July 7, 2007 were eligible for inclusion, because a complete dataset for stones analyzed during that time period was available. Uroliths that were 70% or more urate or uric acid were grouped as 'urate' for analysis. Urethral plugs, sediment, ureteral stones, and nephroliths were excluded from analysis. Mixed uroliths of struvite and urate were not classified as urate stones.

Statistical analysis

The prevalence of urate urolithiasis was described. Categorical comparisons were performed using a chi-squared test. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Wilcoxon's test was used to evaluate the association between age and urate urolithiasis. Logistic regression was used to evaluate the association between urate urolithiasis and urine pH and urine specific gravity. A P-value < 0.05 was considered significant for all comparisons.

Table 2. Feline urate urolithiasis and age

	Age in years: Mean $\pm S_{\bar{x}}$ (range)	Egyptian Mau Mean $\pm S_{\bar{x}}$
Urate submissions	6.3 ± 0.17 (0.4–17)	4.5 ± 0.61 ($P = 0.038$)
Non-urate submissions	7.1 ± 0.039 (0.16–24)	4.8 ± 0.7 ($P = 0.0069$)

$S_{\bar{x}}$ — standard error.

Results

Uroliths from 10 083 cats were examined during the study period. Urate uroliths were identified in 398 (3.9%) cases, including 385 ammonium urate and 13 uric acid. Among the 398 urate stoneformers, 231 (58%) were male and 167 (42%) were female, with urate uroliths identified in 231/5053 (4.6%) of submissions from males and 167/4627 (3.6%) of submissions from females ($P = 0.024$). However, females may be at higher risk for struvite uroliths (2494 struvite submissions from females compared with 1870 from males in the current study). Since this has the potential to create a bias towards false classification of increased risk of other uroliths types in males, analysis was repeated excluding struvite uroliths, and this identified no significant association between gender and urate urolithiasis ($P = 0.73$). The prevalence of urate urolithiasis was highest in Egyptian Maus at 82% (14 urate/17 total urolith submissions), which is significantly higher when compared with all other breeds combined (398/10 083, 3.9%, $P < 0.001$, OR = 118, 95% CI = 38.2 to 510). Birman and Siamese cats were also both significantly over-represented compared with all other breeds combined, with urate uroliths accounting for 3/11 (27%) of total Birman urolith submissions ($P < 0.001$ OR = 9.1, 95% CI = 2.0 to 32) and 25/190 (13%) of total Siamese urolith submissions ($P < 0.001$, OR = 3.9, 95% CI = 2.5 to 5.9). There was no significant association between urate urolithiasis and any other breed. Table 1 summarizes urate and struvite submissions according to gender and breed prevalence.

There was an association between urate urolithiasis and age ($P < 0.0001$). The mean age of cats with urate urolithiasis was 6.3 ± 0.17 y (mean $\pm S_{\bar{x}}$) (range 0.4–17 y) compared to 7.1 ± 0.039 y for non-urate stone formers. Egyptian Maus were significantly younger compared with other breeds combined among all stoneformers (4.8 ± 0.7 y versus 7.1 ± 0.038 y,

$$\text{Purines} \rightarrow \text{Hypoxanthine} \xrightarrow{\text{XO}} \text{Xanthine} \xrightarrow{\text{XO}} \text{Uric acid} \xrightarrow{\text{UC}} \text{Allantoin}$$

Figure 1. Purine metabolic pathway (XO – xanthine oxidase; UC – Uricase).

$P = 0.0069$) and among urate stone formers (4.5 ± 0.61 y versus 6.3 ± 0.18 y, $P = 0.038$). Siamese cats were not significantly younger than others among all urolith types ($P = 0.91$), non-urate uroliths ($P = 0.34$), or urate uroliths ($P = 0.08$). Table 2 summarizes feline urate urolithiasis and age.

There was no association between urine pH and urate ($P = 0.11$), nor was there an association between urate uroliths and urine specific gravity ($P = 0.70$).

Discussion

This study identified significant associations between breed and urate urolithiasis. The higher prevalence of urate urolithiasis in Siamese cats in this study is consistent with prior reports (3,6); however, the association between urate urolithiasis and the Egyptian Mau and Birman breeds is, to the authors' knowledge, a new finding. The astounding association (OR 118) between Egyptian Maus and urate urolithiasis requires further study. It is possible that this breed, and perhaps the Birman and Siamese breeds, have a genetic predisposition for urate urolithiasis, as do dalmatian dogs. In dalmatians, an autosomal recessive mutation leads to alterations in both the hepatic and renal pathways with a decreased rate in conversion of uric acid to allantoin and renal reabsorption of uric acid (Figure 1) (18–20). In addition, the urinary excretion of Tamm-Horsfall protein and glycosaminoglycans in hyperuricosuric, stone forming dalmatian dogs is lower than in non-stone forming dalmatian dogs (21). Recently, a missense mutation in a specific urate transporter gene was identified, and the mutation appears in other breeds with hyperuricosuria (22,23). No investigation of a mechanism for urate urolithiasis has been reported in cats; however, the strong association between breed and urate urolithiasis indicates that studies directed at identifying the mechanism(s) of urate urolithiasis in these breeds are required. It has been reported that the North American Egyptian Mau population is derived from a single imported breeding pair (24), increasing the suspicion of a heritable link to urate urolithiasis tendencies.

An overrepresentation of male cats was identified among urate stoneformers in this study; however, this result must be considered in the context of overall differences between urolith trends in males and females. Male cats are more likely to develop calcium oxalate uroliths and females are more likely to develop struvite (3,6), although the percentage of struvite-containing stones from female cats has decreased significantly in recent years (6). The etiology for the predisposition of female cats and struvite urolithiasis has not been determined. In this study, while an association between males and urate uroliths was initially present, there was no longer a significant association when struvite uroliths were removed from the analysis. This initial association more likely represents the effect of the increased risk of struvite urolithiasis in females rather than the male gender being truly at increased risk of urate urolithiasis. To properly study that aspect, population incidence data would be required, comparing the incidence of urate uroliths between males and females as opposed to the proportion of urate uroliths to total uroliths. Further study of gender association is required.

In contrast to the study by Cannon et al (6), an association between urate urolithiasis and age was identified in this study. It is possible that the larger population size in this study (10 083 versus 5230) facilitated detection of this difference. Cats with urate urolithiasis were significantly younger than non-urate stoneformers, and, in particular, Egyptian Maus were significantly younger compared with cats forming all other types of stones and those forming urate stones. The significant association of younger age and urate urolith formation noted here is consistent with studies reporting the occurrence of metabolic uroliths (urate, cystine, xanthine) in middle-aged cats (4 to 6 y) (3). This also provides further support to the hypothesis that there may be an underlying genetic metabolic defect in certain cat breeds that predisposes the formation of urate uroliths.

Portovascular anomalies, microvascular dysplasia, and any form of severe hepatic dysfunction may predispose to feline and canine urate calculi (25–27). The retrospective nature of this study did not permit identification of cases with concurrent portovascular anomalies; however, a higher incidence of such anomalies in Egyptian Maus, Siamese, or Birman cats has not been reported either in the literature or, to the authors' knowledge, anecdotally. Further studies should evaluate the potential of these conditions on urate stone formation in these predisposed breeds.

Limitations of the current study include its retrospective nature and use of a database for data acquisition. Not all veterinarians submit uroliths for analysis to the CVUC, and those that do may not fully complete the accompanying submission questionnaire. None of these factors would be expected to have a significant effect on the incidence of either overall or breed-specific urate uroliathiasis. Relying on a database of uroliths that were surgically removed results in false elevation of the overall prevalence of uroliths types that are not able to be dissolved using dietary management. Therefore, the prevalence of urate urolithiasis is the prevalence of urate uroliths among surgically removed uroliths, not necessarily the overall prevalence of uroliths among all cats with urolithiasis. The rarity of Egyptian Maus and Birmans must be considered as a potential bias. With a small number of individuals from these breeds, ARTICLE

there is the possibility that management (dietary) practices of 1 owner or small group of owners could result in clustering of cases and that management practices was somehow associated with an increased incidence of urate urolithiasis. However, all Egyptian Mau cases had different owners, and were submitted by different veterinarians.

In conclusion, the relationship between urate urolithiasis and Siamese cats has been previously identified, but the association for Egyptian Mau and Birman cats was remarkable and not previously reported. The significantly younger age of urate stone formers overall, and Egyptian Maus in particular, may indicate a genetic predisposition for urate urolithiasis, and further study of these apparently predisposed breeds is needed. Similarly, gender predisposition requires further study. While only accounting for a small percentage of feline uroliths, urate urolithiasis still accounts for significant morbidity in cats because of the commonness of urolithiasis. Identification of risk factors is an important aspect in elucidating the pathophysiology of urate urolithiasis and identifying potential measures to reduce the incidence of disease. CVJ

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